1998 Equivalence of Sensory Responses to Single and Mixed Volatile Organic Compounds at Equimolar Concentrations

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Exposure to low levels of chemicals indoors is often to a mixture of volatile organic compounds (VOCs). It is of interest to determine if the symptomatic and sensory responses can be attributed to a single chemical or to a mixture of chemicals. To determine if sensory or symptomatic responses differ with exposure to single or mixed VOCs, 100 female subjects participated in a 6-hr exposure study. Subjects were exposed to one of six equimolar concentrations equivalent to 24 mg/m^3 toluene, control, *m*-xylene, *n*-butyl acetate, *m*-xylene plus *n*-butyl acetate, a mixture of 21 chemicals including *n*-butyl acetate and *m*-xylene, and to the same mixture of chemicals without *n*-butyl acetate and *m*-xylene (19 chemicals). The results indicated that there was no difference in reporting of symptoms or sensory responses between the exposures. When the control group was added, some variables, primarily odor intensity and nasal irritation, attained significance. *Key words*: health symptoms, indoor air, irritation, odor, sick building syndrome, volatile organic compounds. *Environ Health Perspect* 106:739–744 (1998). [Online 22 October 1998] *http://ehpnet1.niehs.nih.gov/docs/1998/106p739-744prah/abstract.html*

Volatile organic compounds (VOCs), which originate from diverse sources such as paints, insulation, wood products, carpets, polishes, cleaning products, insecticides, photocopy equipment, and tobacco smoke, contribute to indoor air pollution. The levels of VOCs reported in homes can be quite variable. Otson et al. (*1*) reported a VOC concentration range of <1–104 µg/m^3 in Canadian homes. In a study of U.S. homes, the maximum concentration of VOCs in the indoor air was 16.6 mg/m^3 during the night and 367.1 mg/m^3 during the day (*2*). Other studies (*3,4*) have linked variations in VOC levels to hobbies and cigarette smoking, respectively. Levels of VOCs can be elevated when common activities are performed in the home. For example, data on VOC emission rates from wood-finishing products (stains, polyurethane varnish) showed that during and following the application of these products in an unventilated home, consumers could be exposed for 4–6 hr to concentrations of total organic compounds as high as 1,000 mg/m^3. With ventilation the indoor VOC concentration was halved to 500 mg/m^3 and remained at this level for several hours. Depending on ventilation conditions, the concentration of total organic compounds 16–24 hr after the application of a product was still about 50 mg/m^3 (*5*).

Health symptoms by some building occupants have been attributed to exposure to indoor air pollution. A constellation of symptoms, including mucous membrane irritation, headache, mental fatigue, nausea, dizziness, pulmonary effects, and nonspecific hyperreactivity reactions, has been called sick building syndrome (SBS) (*6*). The SBS symptoms seem to be independent of the putative source, which may include chemicals, pesticides, biological agents, air parameters, or a combination of these factors. The percentage of persons reporting symptoms varies across buildings but, in general, women report symptoms at a higher rate than men (*6–10*).

Among the responses most often reported are irritation of the eyes, nose, and throat (*11*). Eye irritation is among the top five categories of complaints associated with SBS (*12–14*), with complaints from 12–48% of the reporting population (*13,14*).

In controlled chamber studies, sensory effects have been reported by several investigators. Molhave et al. (*15*) exposed persons who reported SBS symptoms to a mixture of chemicals found at ambient levels in new Danish homes. These exposures produced mainly sensory effects. Similar findings were reported (*16,17*) when 66 normal male subjects were exposed to the same VOC mixture at 25 mg/m^3 for 2.75 hr. These subjects reported mild irritation of the eyes and throat but not the nose. A principal complaint, however, was degradation of air quality, which probably encompassed both olfactory as well as trigeminal stimulation. Measures of central nervous system function such as reaction time, digit span, or coding were not affected (*16*). These data are consistent with those reported by Molhave et al. (*15*).

The chemical environment of indoor air is complex because it is typically a mixture of VOCs often dominated by one or more chemicals. For example, Hawthorne et al. (*18*) presented data in which 4 of the 17 chemicals found in the control homes made up 69% of the mixture. Symptoms or sensory responses could be driven by the total mixture or by one or more of its components. The determination of the efficacy of single compounds or mixtures in the production of sensory and symptomatic responses may direct remediation processes more appropriately. To examine this issue, we used a mixture that typifies the chemical environment of new Danish homes (Appendix 1) which has been used in several controlled chamber studies (*15–17*). This mixture is dominated by xylene and butyl acetate, which together constitute 65% of the mix. There are a number of ways to address this question, but equimolar concentrations that equate the exposures on a molar basis were determined to be the most appropriate regimen. The objective was to determine if single chemicals or mixtures of chemicals at equimolar concentrations are more effective at producing sensory responses. This determination may guide remediation strategies in targeting the appropriate sources of VOCs.

Methods

Subjects. The subjects were normal, healthy females with a mean age of 25.1 years. They were nonsmokers with no history of allergy, pulmonary disease, chemical sensitivity, or other serious disease. Females were selected as subjects because they tend to report symptoms at a higher rate than do men. Subjects were tested for allergies with a skin test and for pregnancy on the day of the exposure. All subjects received a physical examination, completed the Minnesota Multiphasic Personality Inventory, and were paid for their participation. Subjects were asked not to wear contact lenses and to refrain from taking analgesics, anti-inflammatory drugs, or vitamin supplements for 48 hr before the exposure. Informed consent was obtained for each subject before participation, and the protocol

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Experimental design. Because this was a between-groups design, each subject was exposed once. A between-groups design was selected to avoid the complexity of scheduling and subject loss. Up to six subjects were tested simultaneously, and the order of exposure for the subjects was randomly selected. Based on previous studies with this mixture (*16,17*), there was no expectation that subjects would report symptoms such as cough, cognitive impairment, or nausea. The null hypothesis was that there is no difference in response to odor and irritation questions due to exposure condition. We used SYSTAT version 6.0 for DOS (SPSS, Chacago, IL) for repeated-measures-over-time analysis of variance. A Greenhouse-Geiser p-value of 0.05 was considered significant.

Exposure. Sixty-five percent of prototype mix (Appendix 1) was equally divided between xylene and butyl acetate, and the remaining 19 chemicals in varying proportions constituted the remaining 35% of the mix. A parsimonious division of the original mix into five exposure conditions and a control condition was all 21 chemicals, 19 chemicals (except *m*-xylene and *n*-butyl acetate), equal parts *n*-butyl acetate and *m*-xylene, *n*-butyl acetate alone, *m*-xylene alone, and a clean-air control. The five exposure conditions were equivalent to 24 mg/m^3, which is the level found in new Danish homes (*15*).

Safety. None of the chemicals were classified as known or possible human carcinogens by EPA's Integrated Risk Information System. Chemicals were presented at concentrations well below the 8-hr threshold limit values (TLVs) established by the American Conference of Government Industrial Hygienists (*19*). Neither *n*-butyl acetate nor *m*-xylene, the dominant chemicals, have unusually low odor thresholds or unusually negative hedonics. The odor thresholds for these chemicals are similar: 1.1 ppm (4.79 mg/m^3) for *m*-xylene and 0.39 ppm (1.86 mg/m^3) for butyl acetate (*20*). Of the rest of the chemicals, none has an exceptionally low threshold. The thresholds ranged from 0.016 mg/m^3 for α-pinene to 234 mg/m^3 for hexane (*21*).

VOC calibration control. The original mixture was 1.17354 moles and was equivalent to 24 mg/m^3 toluene in the chamber atmosphere. Because a flame ionization detector (FID) is essentially a carbon counter, the molar target, 1.17354, was converted to the number of moles of carbon for each exposure. Because more carbons produce a greater FID response, an FID response equal to 29.95 mg/m^3 for xylene (8 carbons) is equivalent to 24 mg/m^3 of the mixture of 21 chemicals, as is a butyl acetate (6 carbons) response of 17.77 mg/m^3, even though they are equimolar. The other exposure conditions were similarly determined and controlled. The chamber concentration for each exposure was 24.0 for the mixture of 21 chemicals, 23.73 for the mixture of 19 chemicals, 24.14 for the mixture of butyl acetate and xylene, 17.77 for butyl acetate alone, and 29.95 for xylene alone. The exposure chemicals were flash evaporated at 250°C in a nitrogen atmosphere, mixed with air, and passed into the plenum of the 3,000-ft^3 stainless-steel exposure chamber. The chamber atmosphere was maintained at 24°C and 40% relative humidity. Chamber variables were all computer controlled, and the exposure concentration was monitored by an FID and controlled to ±3% of target.

Procedure. To maintain double-blind conditions subjects were told that they could be exposed to any one of the six exposure conditions and that the research staff interacting with the subjects had no knowledge of the exposure schedule. Assignment to exposure group was random. The subjects were told that these chemicals were typically found in the indoor environment, that they were below the recommended safety levels, and that none were known or suspected carcinogens. The participants were asked not to discuss the experiment or their responses with the other subjects. Subjects were asked to respond in three formats about their sensory experience or symptoms. These formats were magnitude estimation, categorical, and visual analog (Appendix 2).

To complete the magnitude estimation (*22*) consisting of questions about odor and irritation strength, subjects were asked to sniff a bottle of pure toluene and 5% acetic acid to provide sensory anchors and standards for magnitude estimation of odor strength and nasal irritation, respectively. Subjects were asked to regard the odor and irritant as an intensity of 100 and rate the chamber atmosphere odor and irritation in multiples of 100. For example, if the odor strength in the cham-

Table 1. Statistical analyses of the responses of each of the exposure regimens without the inclusion of the clean-air control group

Question[a]	Exposure		Time		Time by exposure	
	F	*p*	*F*	*p*	*F*	*p*
1. Odor strength (magnitude est)	0.993	0.417*	42.511	<0.000	0.944	0.507*
2. Nasal irritation (magnitude est)	1.240	0.301*	18.110	<0.000	1.463	0.115*
3. Odor intensity (analog)	0.574	0.683*	44.327	<0.000	1.052	0.397*
4. Odor pleasantness (analog)	1.130	0.348*	20.364	<0.000	0.942	0.533
5. Eye irritation (analog)	0.036	0.997	0.625	0.692	0.845	0.666
6. Nasal irritation (analog)	1.984	0.105*	7.386	<0.000	1.261	0.192
7. Throat irritation (analog)	0.725	0.577	0.356	0.846	1.037	0.417
8. Headache (analog)	0.245	0.912	1.036	0.397	1.074	0.374
9. Air quality (analog)	0.548	0.701*	18.402	<0.000	1.335	0.174*
10. Air quality (binary)	0.876	0.482*	5.571	<0.000	1.293	0.170
11. Headache (category)	0.488	0.744	4.385	0.001	0.904	0.579
12. Nasal irritation (category)	2.032	0.098*	4.447	0.001	1.285	0.181
13. Cough (category)	1.364	0.254	0.616	0.658	0.918	0.551
14. Chest tightness (category)	2.125	0.085	0.940	0.445	0.773	0.725
15. Dry eyes (category)	0.164	0.956	0.489	0.001	1.172	0.278
16. Tired eyes (category)	1.712	0.156	4.103	0.004	0.707	0.774
17. Burning eyes (category)	0.075	0.990	2.193	0.056	0.844	0.656
18. Throat irritation (category)	0.658	0.623	0.674	0.584	1.293	0.215
19. Memory (category)	NV		NV		NV	
20. Dry throat (category)	0.394	0.812	0.811	0.531	1.364	0.146
21. Sore throat (category)	NV		NV		NV	
22. Depressed (category)	NV		NV		NV	
23. Unusual fatigue (category)	1.298	0.278	3.778	0.006	0.818	0.662
24. Stuffy nose (category)	0.700	0.595	0.926	0.455	1.015	0.441
25. Tension (category)	0.383	0.820	0.406	0.796	1.142	0.317
26. Back pain (category)	1.653	0.169	5.484	0.001	1.035	0.418
27. Skin rash (category)	NV		NV		NV	
28. Sneezing (category)	NV		NV		NV	
29. Dizziness (category)	0.696	0.597	1.021	0.404	1.111	0.335
30. Mental fatigue (category)	1.410	0.238	2.872	0.030	1.049	0.405
31. Pain in hands (category)	NV		NV		NV	
32. Dry skin (category)	0.682	0.607	0.899	0.448	1.210	0.272
33. Odor strength (category)	1.593	0.184*	33.963	<0.000	1.252	0.207*
34. Air quality (category)	0.331	0.857*	16.903	<0.000	1.495	0.086*
35. Odor pleasantness (category)	1.142	0.343	9.764	<0.000	1.142	0.303

NV, no variability in the data; est, estimation.

[a]Magnitude est, analog, binary, and category indicate the question format.

*Statistically significant when the clean-air control group is added to the analyses ($p = 0.05$).

ber was half as strong as the anchoring odorant, they should provide the number 50; 1.5 times as strong would result in a response of 150. Sensory and symptom data were computer collected at following intervals: preexposure baseline, 0, 20, 40, 60, 120, 180, 240, 300, and 360 min after the subject entered the chamber. Approximately 1 min lapsed between sampling the sensory anchors for the magnitude estimation questions and responding to the baseline questionnaire (0 time point). The categorical questionnaire (Appendix 2) has been used in a large-scale SBS study (*14*). The subjects were also asked to rate the air quality and sensory effects of the chamber atmosphere by positioning a pointer on a visual analog scale presented on a computer screen. The scale ranges were, for example, "no irritation" and "unacceptably strong irritation" (Appendix 2). Following the acquisition of clean air baseline questionnaire data, the subjects left the chamber while the exposure atmosphere was initiated and stabilized. After the conditions stabilized the subjects again sniffed the toluene and acetic acid to reacquaint themselves and reentered the chamber to begin the 6-hr exposure by completing the next questionnaire. Subjects entered the chamber in approximately 20-min intervals because the time required for the exploratory eye testing (about 20 min) would delay the start of the exposure if all subjects entered the chamber simultaneously. Subjects were permitted to read, converse, or watch television. Two to six subjects participated in each session.

Pilot methods development. Measures of tear film break-up time, conjunctival epithelial damage, and eye redness (ocular hyperemia) were obtained before the start of the experiment and again upon completion of the exposure period. These data will be reported in a separate paper.

Results

One hundred subjects participated in the experiment; 15 in the mixture of 21 group, 16 in the mixture of 19 group, 20 in the *n*-butyl acetate plus *m*-xylene group, 16 in the *n*-butyl acetate group, 17 in the *m*-xylene group, and 16 in the clean-air control group. Table 1 displays the results of the analysis of the questionnaire responses of the exposure groups. No significant effects of exposure were evident on any item, indicating that there was no difference between ratings of the five exposures. Significant time effects (Fig. 1), which reflected sensory adaptation, were observed for the olfactory (questions 1, 3, 4, 33, 34, and 35) items regardless of the question format (magnitude estimation, analog, or categorical). A linear trend accounted for most of the sum of squares. The absence of a significant time-by-exposure interaction indicated that there was no difference between the chemical exposures in adaptation rate. Responses to questions about nasal irritation (questions 2, 6, and 12) followed a similar pattern to olfactory endpoints in that there was a significant time effect, but no time-by-exposure effect (Fig. 2) or exposure effect. Responses to the air quality questions (questions 9 and 10) similarly reflected adaptation. In this case, as the experiment progressed, the perceived air quality improved as olfactory strength declined (Fig. 3). Ratings of ocular and throat irritation (questions 5, 7, 18, and 21) were not different between exposure conditions and showed no significant changes with time. Even when the control condition was added to the analyses, no statistical differences emerge for ocular or throat irritation. Fatigue (questions 23, 26, and 30) increased significantly during the experiment. No health-related effects such as cough, chest tightness, dry throat, sore throat, stuffy nose, skin rash, sneezing, pain, or dry skin (questions 13, 14, 20, 21, 24, 27, 28, 31, and 32, respectively) were reported. No evidence of cognitive impairment, memory loss, depression, tension, or dizziness was recorded (questions 19, 22, 25, and 29, respectively). When data from the control group were added to the analysis, some of the response variables did attain statistical significance, as shown in Table 1.

Although the primary goal of this experiment was to determine if there were differences

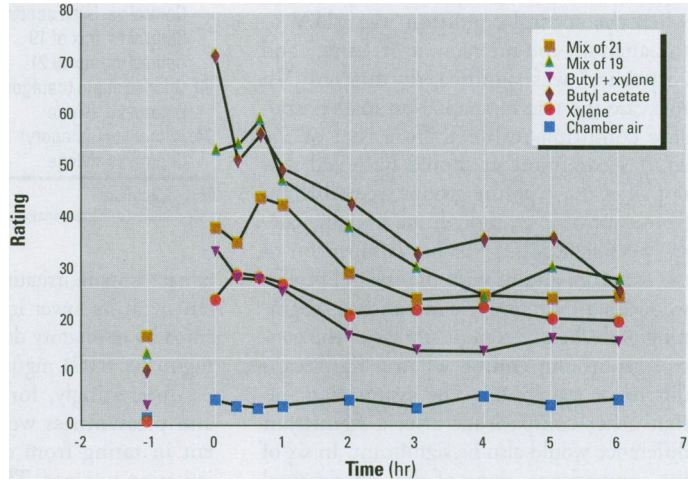

Figure 2. Adaptation to irritation from chemical exposures. As can be seen, reported irritation initially rises then declines as the exposure progresses. Baseline data were obtained at the -1 time point.

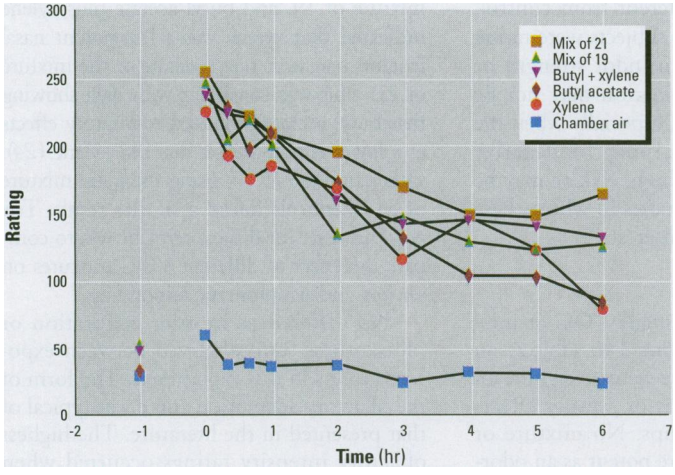

Figure 1. Olfactory adaptation to the various exposure conditions. Differences between the control and exposure conditions were significant, but the differences between the exposure conditions were not significant in magnitude or rate of adaptation. Baseline data were obtained at the -1 time point.

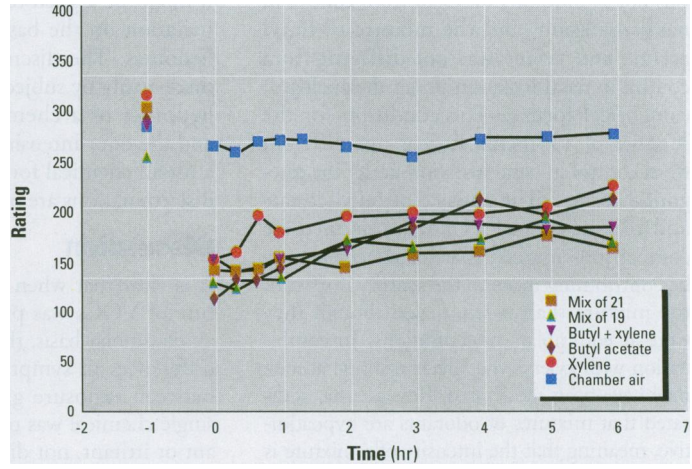

Figure 3. In comparison with olfactory adaptation (Fig. 1), it can be observed that as odor intensity declines, air quality improves. Baseline data were obtained at the -1 time point.

in responding between the equimolar exposures, the addition of the clean-air control group permitted further comparisons. When the control group was added to the repeated-measures analyses (Table 1), significant differences were obtained on some response measures, notably odor intensity, nasal irritation, air quality, and odor pleasantness. These results are presented in greater detail in Table 2. As shown in Table 2, "exposure," "time," and "time by exposure" differed significantly under these analytical conditions. Significant differences indicated that the VOC-exposed group rated their experience as 1) more irritating to the nose, 2) having a greater odor strength, 3) having reduced air quality, and 4) as less pleasant than to the control group. Responses to the items in Table 2 differed in "time," implying that there was a significant difference in responding over the 6-hr exposure. This change over time was rate of adaptation. Significant "time by exposure" implied that when the control condition was added to the analysis, the interaction of "time" and "exposure" was significantly different. In this case the rate of adaptation to the exposure conditions differed from that of the control condition. It should be noted that not all of the exposure groups were different from control, even though the overall analyses were significant. Further comparison of the exposure groups with the control groups were done by iterative comparisons, beginning with the mean most similar to the control group and ending when a significant difference was found. The assumption was that other comparisons after a significant difference would also be significant. In six of the comparisons, none of the experimental groups were different from control.

In 4 of the 10 questions xylene was not significantly different from the control exposure. Regardless of question format, xylene was not significantly different from control in nasal irritation, and the mixture of butyl acetate and xylene was not different from control in nasal irritation under the analog or categorical format. The condition for the mixture of 19 chemicals was not different from control in nasal irritation under the categorical format. The absence of butyl acetate and the mixture of 21 chemicals in these comparisons implied that butyl acetate may be contributing more to the sensory impact of the mixture than xylene, even though they were at equimolar concentrations. In combination with xylene, the effects of butyl acetate may have been moderated. Research has indicated that mixtures of odorants are hypoadditive, meaning that the intensity of a mixture is less than the sum of the intensity of the individual components (*23*). This finding may apply to nasal irritation as well. That butyl acetate is more irritating than xylene is consistent with its lower irritant potency, as measured by respiratory depression in mice (3,475 mg/m^3 vs. 6,091 mg/m^3, respectively (*24*).

Table 2. Statistical analyses of the questions that were significantly different when the control group was added to the analyses (p = of 0.05)

	Exposure		Time		Time by exposure	
Question[a]	F	p	F	p	F	p
1. Odor strength (magnitude est)	4.460	0.001	40.986	<0.000	2.239	0.004
Control vs. butyl acetate + xylene	46.421	<0.000	13.204	<0.000	9.543	<0.000
2. Nasal irritation (magnitude est)	2.879	0.018	17.127	<0.000	2.095	0.004
Control vs. xylene	3.725	0.063	0.478	0.660	0.903	0.427
Control vs. butyl acetate + xylene	15.143	<0.000	3.415	0.017	0.140	0.007
3. Odor intensity (analog)	11.039	<0.000	43.69	<0.000	1.965	0.003
Control vs. xylene	31.355	<0.000	9.983	<0.000	4.390	0.003
4. Odor pleasantness (analog)	5.036	<0.000	19.963	<0.000	1.438	0.041
Control vs. Butyl acetate + xylene	9.886	0.003	3.724	0.010	2.597	0.048
6. Nasal irritation (analog)	2.694	0.025	6.663	0.000	1.353	0.106
Control vs. xylene	0.390	0.534	2.377	0.045	1.448	0.213
Control vs. butyl acetate plus xylene	1.618	0.212	0.826	0.476	0.637	0.583
Control vs. butyl acetate	4.684	0.039	2.755	0.035	2.981	0.025
9. Air quality (analog)	4.900	<0.000	17.919	<0.000	1.684	0.031
Control vs. xylene	8.313	0.007	3.751	0.008	1.807	0.138
10. Air quality (binary)	2.542	0.033	5.488	<0.000	1.445	0.069
Control vs. xylene	3.485	0.071	0.455	0.886	0.455	0.886
Control vs. butyl acetate	8.050	0.008	1.815	0.134	1.815	0.134
12. Nasal ilrritation (category)	2.925	0.017	3.757	0.002	1.344	0.125
Control vs. xylene	1.181	0.285	0.781	0.533	0.520	0.711
Control vs. butyl acetate + xylene	1.692	0.202	0.295	0.790	0.898	0.429
Control vs. mix of 19	3.390	0.057	1.865	0.135	2.680	0.046
Control vs. mix of 21	12.488	<0.001	1.340	0.261	1.241	0.276
33. Odor strength (category)	10.837	<0.000	33.135	<0.000	1.636	0.025
Control vs. xylene	19.149	<0.000	5.200	<0.000	1.976	0.076
34. Air quality (category)	2.888	0.018	18.675	<0.000	1.613	0.036
Control vs. xylene	4.432	0.043	6.669	<0.000	2.282	0.077

est, estimation.
[a]Magnitude estimation, analog, binary, and category indicate the question format.

Interestingly, for xylene, odor strength and pleasantness were significantly different in rating from control, whereas nasal irritation was not. These data illustrate that subjects can discriminate nasal irritation from other effects of the chemicals such as odor intensity and hedonics. Had nasal irritation not been different from control, it might be argued that subjects were rating irritation on the basis of odor strength or hedonics. The discrimination may not be made easily by subjects, especially when the hedonics of a chemical may be negative and the odor intensity high. Xylene may be a useful chemical for studies in which these discriminations are of interest.

Discussion

It is clear that when a single VOC or mixture of VOCs was presented to subjects on an equimolar basis, there were no significant differences in symptoms or sensory effects between exposure groups. No mixture or single chemical was more potent as an odorant or irritant, nor did adaptation rate differ with chemical or mixture. These results imply that when subjects were exposed to single chemicals or mixtures that do not have particularly negative odor hedonics or were not strong irritants, little differential responding was recorded. Health-related symptoms were not significantly different between exposure conditions.

When compared to the clean-air control group, significant overall differences were observed in some response categories such as odor intensity, nasal irritation, and air quality, but not health effects. The absence of significant differences between the control, xylene, mixture of 19, and butyl acetate plus xylene indicated that xylene was a less potent nasal irritant than were butyl acetate or the mixture of 21. This was consistent with data showing that butyl acetate produced respiratory effects at a lower concentration that did xylene (*24*). Other studies (*15,17*) using the same mixture of 21 chemicals found a similar result. The goal, however, in this experiment was to compare the effect of different VOC mixtures on sensory and symptomatic responding.

No differences in odor adaptation or pleasantness were observed between exposure groups in this experiment. The form of the olfactory adaptation curve was typical of that presented in the literature. The highest olfactory intensity ratings occurred when the subject entered the chamber, and they gradually declined to about 40% of the initial value at the end of the 6-hr exposure. This adaptation curve was like that of the

neutral bias condition presented by Dalton (*25*), in which subjects were biased by positive, neutral, or negative information about the experimental exposure. Interestingly, subjects in Dalton's negatively biased condition showed initial adaptation, followed by an increase in reported odor intensity, while those in the positive bias condition showed greater adaptation than the negative or neutral bias conditions. Though symptoms were not the primary focus of Dalton's study, 11 of the 13 subjects spontaneously reporting symptoms were in the negative bias condition. Thus, instruction and expectation can have a powerful effect on the outcome of an experiment. Likewise, expectation may have influence on the self-reports from sick building inhabitants who think that their workplace represents a toxic exposure and attribute physical or psychological discomfort to their perceptions of the safety of their work environment independent of any toxic effect of the chemical exposure. Environmental odors may serve a semiotic role to which people relate their experiences and when experienced again guide their behavioral responses. Thus, odors may summarize the complex qualities of a work situation (*26*).

In contrast to other reports exposing subjects to the same mixture for a briefer time period, 2.75 hr (*15,17*), adaptation to irritation was observed in the trigeminally innervated nasal but not ocular or pharyngeal mucosas. In the Hudnell et al. (*17*) study, responses to ocular, nasal, and pharyngeal irritation were combined to constitute the dependent variable. Adaptation reported in the present study was preceded by an initial increase in irritation and was consistent with data presented by Cain et al. (*27*), who exposed subjects to formaldehyde in a chamber and with data of Elsberg et al. (*28*), who showed adaptation to nasal irritation of oil of cade (juniper) and turpentine. Adaptation to trigeminally mediated irritation does not begin immediately after the onset of exposure as in olfaction, but follows a period of increased irritation. Adaptation was not complete but remained at an asymptotic level for the final 3 hr of exposure. Like olfaction, at the 6-hr point the rated nasal irritation averaged about 40% of the initial values. In the present study, the greater duration of exposure provided adequate time for as much adaptation in irritation as in olfaction to be observed. It is likely that trigeminal adaptation can be influenced by the perceived toxicity of the exposure in a similar manner to that reported by Dalton (*25*) in olfaction. Indeed, in another study Dalton et al. (*29*) reported that in a positive bias condition, subjects exposed to 1,967 mg/m^3 acetone reported significantly less irritation and fewer health symptoms than those in the neutral or negative bias condition.

In the present study, failure to observe differential sensory and symptomatic responses between exposures and the presence of adaptation may be attributable to the absence of stress in the testing environment. Subjects were given assurances in the consent form that the chemicals in the mixture were commonly found in the indoor environment at typical levels below established occupational standards. Such information would be similar to the information in the neutral bias condition discussed above (*25,29*). Displaying sensitization or failing to adapt may be a consequence of the cognitive processing of chemical exposure information in a laboratory or a sick building situation. Working in a sick building may engender stress, which has been reported to prevent olfactory adaptation in women (*30*). Morris and Hawkins (*31*) reported that in sick buildings there was a higher complaint rate of stress or tension among those who report sick building syndrome symptoms. Failure to show trigeminal or olfactory adaptation may be part of the adaptive sympathetic response to a stressful situation.

The absence of differences in rated odor pleasantness implies that there was no difference in hedonics between the exposures. These findings will be of importance to those seeking the source remediation of the "sickness" of a building. Because quantitative analyses are much less expensive than qualitative analyses, it may be more important to determine the total hydrocarbon load rather than the actual VOC components in the building environment. Reduction of the total VOC load by targeting known sources such as photocopiers may ease the expense of remediation. A chemical with a very low threshold or unpleasant hedonics such as a mercaptan may be an exception to this point. Clearly, to understand sick building syndrome, future chamber experiments should include biasing instructions and/or experimental manipulations such as a stressful task or an uncomfortable physical environment that would engender stress. Understanding the personal variables that result in the absence of sensory adaptation to a low-level or innocuous chemical exposure may be a useful strategy in the understanding of sick building syndrome and identifying those who may be vulnerable to this syndrome.

Appendix 1

Composition of the Mixture at 6.7 ppm (24 mg/m^3)

Chemical	PEL (ppm/mg/m^3)	21 VOCs (mg/m^3)
1. *n*-Butyl acetate	150/71	7.750
2. *m*-Xylene	100/435	7.750
3. *n*-Butanol	100/300	0.775
4. *n*-Decane	No TLV	0.775
5. 1-Decene	No TLV	0.775
6. Ethylbenzene	100/435	0.775
7. Ethoxyethylacetate	100/540	0.775
8. *n*-Hexanal	No TLV	0.775
9. *n*-Hexane	500/1800	0.775
10. *n*-Nonane	200	0.775
11. α-Pinene	No TLV	0.775
12. 2-Butanone	200/590	0.078
13. Cyclohexane	300/1050	0.078
14. 3-Methyl-2-butanone	200	0.078
15. 4-Methyl-2-pentanone	100/410	0.078
16. *n*-Pentanal	50	0.078
17. Isopropanol	400/980	0.078
18. *n*-Propylbenzene	No TLV	0.078
19. 1,2,4-Trimethylbenzene	25/120	0.078
20. *n*-Undecane	No TLV	0.078
21. 1-Octene	No TLV	0.008

Abbreviations: PEL, permissible exposure limit; VOC, volatile organic compound; TLV, threshold limit value.

Appendix 2

Three-Part Questionnaire

Part 1: Magnitude Estimation Questions

1. Rate the odor in the chamber compared to the test odor.
   Test odor is 100;
   If current odor is half as strong use 50;
   If current odor is twice as stong use 200;
   Use any number to accurately reflect the odor level
   Enter number.
2. Rate nasal in the chamber compared to the test irritant.
   Test irritant is 100;
   If current irritation is half as strong use 50;
   If current irritation is twice as stong use 200;
   Use any number to accurately reflect the nasal irritation you feel.
   Enter number.

Part 2: Categorical Questions

Instructions: please indicate if you are experiencing any of the symptoms listed below, using the following scale to indicate the severity of the symptoms.

0 = None (symptom is not present)
1 = Trace (symptom is barely detectable)
2 = Mild (symptom is present, but not annoying)
3 = Moderate (symptom is present, but somewhat annoying)
4 = Severe (symptom is present and very annoying or painful)

3. Headache
4. Irritation of the nose
5. Cough
6. Wheezing, chest tightness, or shortness of breath
7. Dry, itching, or irritated eyes

continued, next page

Appendix 2, continued

8. Tired or strained eyes
9. Burning eyes
10. Irritation of the throat
11. Difficulty in remembering things or concentrating
12. Dry throat
13. Sore throat
14. Feeling depressed
15. Unusual tiredness, fatigue, or drowsiness
16. Stuffy or runny nose, or sinus congestion
17. Tension, irritability, or nervousness
18. Pain or stiffness in back, shoulders, or neck
19. Skin rash
20. Sneezing
21. Dizziness or lightheadness
22. Mental fatigue or "fuzziness"
23. Pain or numbness in the hands or wrists
24. Dry skin
25. Rate the odor level in room
26. Rate the air quality in room (very poor to very good)
27. Rate the odor pleasantness (very bad to very good)

Part 3: Visual-Analog Questions

28. What is the intensity of the odor in the room now?
    No odor ..... Extremely strong
29. How pleasant is the odor in the room now?
    Extremely acceptable ..... Extremely unacceptable
30. Do you feel any eye irritation now?
    Not at all irritated ..... Extremely irritated
31. Do you feel any nasal irritation now?
    Not at all irritated ..... Extremely irritated
32. Do you feel any throat irritation now?
    Not at all irritated ..... Extremely irritated
33. Do you have any headache now?
    No headache ..... Extremely strong
34. How is the air quality in the room now?
    Very good ..... Very poor
35. Is the air quality acceptable now?
    Yes ..... No

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